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Homocysteic Acid Mediates Amyloid Pathogenicity for Cognitive Impairment in Alzheimer's Disease

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Abstract

Recently Alzheimer's Disease Neuroimaging Initiative (ADNI) observation has reported that MCI who has higher level of amyloid decline his cognitive ability faster than MCI who has a relative lower amyloid in his brain. However, in a normal patient's brain in which the amyloid level was almost equal to that of an MCI patient's brain, the cognitive ability was not at all declined. Consequently, a strong debate surrounds the differences between the normal, MCI, and AD patient's brains regarding amyloid toxicity. It is rational that MCI has some unknown factors in which the toxicity is increased in the presence of amyloid, but a normal patient's brain has no such unknown factors. Moreover, we observed that the neurodegenerative effect of homocysteic acid (HA) was significantly higher in MCI than that in a normal patient's brain, and this HA toxicity was enhanced in the presence of amyloid. Therefore, it is highly possible that the previously mentioned unknown factor is HA.

The amyloid hypothesis is a legitimate pathogenic theory in AD, but some modification is required to elucidate the human AD process. Moreover, a novel pathogen containing HA can modify this amyloid hypothesis. Therefore, amyloid induces phosphorylated-tau toxicity by HA, and consequently, amyloid induces the neurodegeneration of AD.

HA can induce neurodegeneration without the presence of amyloid, and AD without amyloid can be induced by HA.

Blood HA in MCI Patients

We have recently determined the blood HA levels in MCI patients and found that the levels are significantly higher than that in normal individuals ($p<0.001$ MCI vs normal patients; n=13 [1].

This blood HA level may induce the disruption of the blood–brain barrier (BBB) and is then able to enter the brain. The extent to which HA enters the brain is unknown; however, our preliminary observations revealed that the HA levels in the cerebrospinal fluid of early MCI patients was approximately 100 nM compared with almost 1 nM of normal patients [1]. These findings suggest that HA of MCI patients can induce neurodegeneration in the presence of amyloid, and consequently, the cognitive decline occurs faster than in normal patients. Because our published data indicates that 1 μM of HA destroyed neurons in the presence of amyloid [2].

Additionally, HA induced alpha-synuclein [3] and this induction were inhibited by a gamma-secretase inhibitor [1], which indicated that HA combined the amyloid and alpha-synuclein toxicity.

The amyloid hypothesis is a pathogenic theory in AD, but some modification is required to determine the human AD process. Moreover, our novel theory of HA pathogenesis is able to modify this amyloid hypothesis. Therefore, amyloid induces the phosphorylated-tau toxicity by HA, and consequently, amyloid induces the neurodegeneration of AD.

HA alone is able to induce neurodegeneration without amyloid, and AD without amyloid should also be induced by HA.

We have observed that AD patients exhibited a positively significant relationship between the MMSE scores and their urinary homocysteic acid levels. Homocysteic acid (HA) is a reported as being pathogenic in a 3xTg-AD mouse model [4]. This HA is excreted actively into the urine. However, when this urinary excretion is suppressed, the HA in the peripheral blood increases, and consequently, could disturb brain function, and the MMSE score would decrease [1].

Homocysteic acid is a well-known glutamatergic neurotransmitter in the field of neurophysiology [5]. However, the physiological role of HA has not yet been elucidated. Recently, Countiho M et al. [5] reported that tonic immobility in a guinea pig model of PGA was controlled by HA. They reported that a stressful event released HA, which controlled immobility in the guinea pig. However, HA is not the usual transmitter. When the beta-adrenergic receptor is activated, HA levels increase and are released from astrocytes [6]. Thus, special conditions are required to release HA, which affects normal neuronal transmission. This special state is similar to stress.

HA Induces Neurodegenerative Toxicity

It has been established that excess glutamate can destroy neurons [7] and HA can achieve neurodegeneration at a micromolar level [3]. Typically, the physiological level of HA is on a nanomolar scale [3]. However, when the brain is specially treated with a methotrexylate drug, HA will be increased by micromolar amounts and destroy the neurons, which consequently induces cognitive impairment [8]. HA results in neurodegeneration, the inhibition of mitochondrial component I, metabolic changes, and lactate production [9,10].

Neurodegenerative Toxicity of HA is related to Alzheimer's Pathology

Alzheimer's pathology is thought to be based on the amyloid cascade hypothesis [11], and HA specifically produces amyloid beta 42.

Neurodegeneration is also related to phosphorylated tau [12]. Moreover, HA induces the alpha-synuclein in the presence of amyloid, and a gamma-secretase inhibitor inhibited this alpha-synuclein production by HA. From these two results, it can be concluded that HA induced amyloid beta 42 and alpha-synuclein production through this production of amyloid beta 42.

HA is a combination of amyloid beta 42 and alpha-synuclein. It is known that theamyloid pathology stimulates the calcium flux [13], which stimulates oxygen radical formation [14] to produce homocysteic acid from homocysteine or methionine. Recently, it has been reported that phosphorylated tau is induced by alpha-synuclein [15]. However, these results were obtained using an in vitro system. Therefore, further clarification of HA pathogenic activity in an in vivo system is required.

Pathogenic Activity of HA in a 3xTg-AD Mouse Model

AD is an age-associated progressive neurodegenerative disorder associated with dementia, the exact pathogenic mechanisms of which remain unknown. We previously reported that HA may be one of the pathological biomarkers in the brains of AD patients. Moreover, the increased levels of HA may induce the accumulation of intraneuronal amyloid beta (Ab) peptides. In this study, we further investigated the pathological role of HA in a mouse model of AD. Four-month-old prepathological 3xTg-AD mice exhibited higher levels of HA in the hippocampus than the age-matched nontransgenic mice. This suggests that HA accumulation may precede both Ab and taupathologies. We then fed 3-month-old 3xTg-AD mice with vitamin B6-deficient food for 3 weeks to increase the HA levels in the brain. Concomitantly, the mice received either saline or anti-HA antibodies intraventricularly via a guide cannula every 3 days while receiving the B6-deficient diet. We found that mice that received anti-HA antibodies significantly resisted cognitive impairment induced by vitamin B6 deficiency and AD-related pathological changes in their brains were attenuated compared with the saline-injected control group. A similar neuroprotective effect was observed in12-month-old 3xTg-AD mice that received anti-HA antibody injections while receiving a regular diet. We concluded that increased brain HA triggers memory impairment, and this condition deteriorates with amyloid and leads to subsequent neurodegeneration in mouse models of AD [2].

From our observations, it was concluded that HA exhibited pathogenic activity in a 3xTg-AD mouse model. These 3xTg-AD mice have three genetic transforms (APP, Presenilin, and Tau) in which the pathogenic process is thought to be induced by APP-, Presenilin-, and Tau-activated genes. Therefore, amyloid is important in 3xTg-AD mice. However, our findings also indicated that pathogenic HA is involved in this detrimental amyloid activity [2].

Pathogenic HA Activity in Humans

HA has been suggested to be pathogenic in a 3xTg-AD mouse model of AD. However, it has not been established whether HA is involved in humans. We investigated the relationship between urinary HA levels and the MMSE scores in patients with AD (n=70) and non-dementia controls (n=36).

We found a positive, statistically significant relationship between the two variables (urinary HA levels and MMSE score) ($r=0.31$, $p=0.0008$, $n=70$). This relationship was stronger in females than in males ($r=0.43$, $p=0.005$, $n=44$ in females; $r=0.48$, $p=0.02$, $n=22$ in males). The urinary HA levels were significantly different in AD patients compared with the controls (AD: 8.7 ± 7.5, $n=70$; non-dementia control: 13.3 ± 9.4, $n=36$, $p<0.01$). In addition, aging and smoking were found to be factors that decreased urinary HA levels. Our preliminary study demonstrated a negative, statistically significant relationship between blood HA (μM) and urine HA levels (mM) ($r=-0.6$, $p=0.007$, $n=19$).

On the basis of these results, we speculate that reduced urinary excretion induces elevated HA levels in the blood, resulting in cognitive dysfunction. This study also suggests that HA may be a type of neurotoxin for uremic encephalopathy. However, it is a question of how blood HA affects cognitive brain function [16].

Other evidence supports pathogenic HA activity in humans

There have been several reports that suggest the involvement of HA in the pathogenic processes of AD. First, Vlassenko et al. [16] have reported the possible link between regional aerobic glycolysis and the amyloid deposition in a normal brain. We believe that this phenomenon may be induced by HA because HA is known to be a neurotransmitter in a normal brain [5] and induces seizures in immature rat pups. In the pup's brain, the metabolism was altered to a stronger glycolysis [10]. Moreover, HA induces the intraneuronal accumulation of Aβ 42 [3] and antibodies of HA attenuate AD pathology in 3xTg mice [2].

Second, it has been reported that the homocysteine-lowering via B vitamins slows the rate of accelerated brain atrophy under conditions of mild cognitive impairment [17]. Moreover, this report suggests that homocysteine induces brain atrophy. However, homocysteine itself has a lower activity of neurodegeneration at a physiological level, and it is unclear what caused the neurodegeneration. HA from homocysteine exhibited this effect.

In a study published in Nature [18,19], Stanford University School of Medicine scientists has found substances in the blood of older mice that can make younger brains act older. These substances, had levels that increased with age and appear to inhibit the brain's ability to produce new nerve cells critical for memory and learning. These findings raise the question of whether it might be possible to shield the brain from aging by eliminating or mitigating the effects of these apparently detrimental blood-borne substances.

APOE4 is the gene involved in the development of AD. APOE4 increases the permeability of BBB [20], which then allows the pathogenesis of the peripheral blood to pass BBB and disturb the brain functionalities. This report indicates the possibility of APOE4 as an early-onset gene. Finally, the third report [21] describes an early AD patient exhibiting signs of destruction in the hippocampal BBB. However, these reports did not describe which factor in the blood was involved and what resulted in the increased BBB permeability in an aged hippocampus.

It has been reported that HA is a probable AD pathogenic factor in the blood [22], and it increases the BBB permeability by NMDA receptor activation of HA [23].

HA Pathogenic Activity Modifies Amyloid Hypothesis

The amyloid hypothesis is thought to be the primary mechanism of Alzheimer's pathology; however, recent findings (especially ADNI) provide a strong debate for the amyloid hypothesis. In particular, ADNI reported that MCI patients who have a higher level of amyloid, decline his cognitive ability faster than MCI who has a relative lower amyloid in his brain [1]. However normal brain whose amyloid level was almost equal to MCI's brain did not decline his cognitive ability at all. It is important to note that amyloid toxicity in a normal brain could not be observed. Therefore, it is easy to think that amyloid has no causative toxicity for normal brain functionality. However, many experiments in mice models found that amyloid did demonstrate a toxic effect on neuronal functions. Thus, it is not understood why amyloid did not demonstrate any harmful effect on the human brain. Naturally, it is likely that there must be other factors to support amyloid toxicity in humans, which may not be present in mice. The other factors in humans, including HA, are as follows: First, mice do not suppress the urinary excretion of HA with age [24], but humans do. This indicates that HA blood levels in humans increase with age, which consequently increases the HA levels in the brain via the

deterioration of BBB permeability by HA. Second, HA produces amyloid beta 42 and this amyloid accumulate in the neurons, which induces alpha-synuclein, and consequently, induces phosphorylated tau. Third, normal brain has very low levels of HA, which facilitates the amyloid-induced phosphorylated-tau toxicity. Therefore, the normal brain does not exhibit amyloid toxicity.

Indeed, amyloid facilitates HA toxicity. However, HA alone can induce neurodegeneration without amyloid. Observations of normal brains indicated that the amyloid alone doesn't appear to be the causative but an enhancer of AD pathology. AD without amyloid also was reported [25], which may be induced by HA.

A recent article has been published [26] that reported a methionine-induced amyloid and phosphorylated-tau pathology in wild type mice that exhibited pathologies typical of AD. This report is interesting because they reported that the heavily oxidizing methionine could induce HA [27]. Therefore, HA is a possible factor in the pathogenesis of AD.

Conclusions

HA is involved in the pathogenesis of AD in both mice and humans. The amyloid hypothesis remains valid, but amyloid toxicity enhances the pathogenic activity of HA in humans.

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